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# Inhibition of stress-activated MAP kinases induces clinical improvement in moderate to severe Crohn's disease.

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BACKGROUND & AIMS: We investigated if inhibition of mitogen-activated protein kinases (MAPKs) was beneficial in Crohn disease. METHODS: Inhibition of JNK and p38 MAPK activation with CNI-1493, a guanylhydrazone, was tested in vitro. Twelve patients with severe Crohn's disease (mean baseline, CDAI 380) wer randomly assigned to receive either 8 or 25 mg/m(2) CNI-1493 daily for 12 days. Clinical endpoints included safety, Crohn's Disease Activity Index (CDAI), Inflammatory Bowel Disease Questionnaire, and the Crohn's Disease Endoscopic Index of Severity. RESULTS: Colonic biopsies displayed enhanced JNK and p38 MAPK activatior CNI-1493 inhibition of both JNK and p38 phosphorylation was observed in vitro. Treatment resulted in diminished JNK phosphorylation and tumor necrosis factor production as well as significant clinical benefit and rapid endoscopic ulcer healing. No serious adverse events were noted. A CDAI decrease of 120 at week (P = 0.005) and 146.5 at week 8 (P = 0.005) was observed. A clinica response was seen in 67% of patients at 4 weeks and 58% at 8 weeks Clinical remission was observed in 25% of patients at week 4 and 42

at week 8. Endoscopic improvement occurred in all but 1 patient. Response was seen in 3 of 6 infliximab failures, 2 of whom showed remission. Fistulae healing occurred in 4 of 5 patients, and steroids were tapered in 89% of patients. CONCLUSIONS: Inflammatory MAPKs are critically involved in the pathogenesis of Crohn's disease and their inhibition provides a novel therapeutic strategy.

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- Randomized Controlled Trial

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